Original Article

# Efficacy of Multimodal Perioperative Analgesia Protocol with Periarticular Medication Injection and Nonsteroidal Anti-inflammatory Drug Use in Total Knee Arthroplasty

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**Abstract**

**Background:** This research examined multimodal analgesia and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for early analgesic effect and rehabilitation after total knee arthroplasty (TKA). **Methods:** A total of 110 patients who were scheduled to undergo TKA were randomly divided into two groups, experimental group and control group. The experimental group received a periarticular multimodal drug injection containing 200 mg ropivacaine, 30 mg ketorolac tromethamine, 0.3 mg epinephrine, and 5 mg hexadecadrol during surgery. The control group received an equal volume of normal saline. All the patients received an analgesia pump and moderate NSAIDs. Resting and motion numeric rating scale (NRS) scores, knee joint range of motion, length of postoperative hospital stay, patient satisfaction, total nonsteroidal anti-inflammatory consumption, and side effects were recorded. **Results:** The experimental group exhibited significant improvement in pain NRS scores during rest and exercise several days postoperatively. The range of joint motion was more flexible in the experimental group, and the length of postoperative hospital stay was shorter (9.25 ± 1.99 days vs. 10.44 ± 2.62 days, $P < 0.05$). Patients in the experimental group consumed fewer NSAIDs (965 mg vs. 1325 mg, $P < 0.05$) and reported greater satisfaction with the surgery. **Conclusion:** Intraoperative periarticular injection with multimodal drugs significantly relieved pain after surgery and reduced the requirements for NSAIDs. This injection also improved patient satisfaction and the range of joint motion with no apparent risks following TKA.

**Keywords:** *Analgesia, arthroplasty, knee, nonsteroidal anti-inflammatory drugs, pain*

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## Introduction

Total knee arthroplasty (TKA) is an important therapy for severe knee joint disease that relieves knee pain and improves knee joint function. Approximately 90% of patients with pain and dysfunction improve after TKA, which also improves their standard of living. Most patients are very satisfied with the curative effect of surgery and postoperative quality of life.[1,2] Postoperative pain has a harmful effect on important organs of patients, and it directly affects postoperative rehabilitation exercises.[3] Ischemia-reperfusion injury and surgical trauma inflammatory reactions caused by the use of a tourniquet also lead to postoperative pain. Pain after TKA increases patients' concerns about rehabilitation exercises, which affects the rehabilitation of the disease. The clinical application of many analgesia methods exhibits limitations.[4-6] Therefore, the identification of an effective and safe analgesic treatment

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is an important challenge. Multimodal perioperative analgesia effectively prevents pain and exhibits a lower systemic side effect profile. This study used a randomized, single-blind study to investigate whether an intra-articular injection of a mixture of ropivacaine, ketorolac tromethamine, dexamethasone, and adrenaline achieved better analgesia and reduced the requirements of nonsteroidal anti-inflammatory drugs (NSAIDs).

## Materials and Methods

### Patient population

Approval was obtained from the Biomedical Ethics Group of the Medical Department of Xi'an Jiaotong University (number 2012-693). Moreover, we have registered the protocol at Chinese clinical trial registry (No. ChiCTR-INR-17012217).

Figure 1 details the patient flow through the study. Baseline covariates were well balanced across the groups [Table 1]. We conducted a prospective, randomized single-blinded study of all eligible men and nonpregnant women who were scheduled to undergo primary TKA for osteoarthritis from September 1, 2012, to November 1, 2015. All patients were at least 30 years of age and no more than 85 years old. The following inclusion criteria were used: (1) The American Society of Anesthesiologists (ASA) Grade I ~ III rating; (2) weight index of 20–35 kg/m$^2$; (3) unilateral TKA; (4) ability to cooperate with the investigation and understand the pain score; and (5) signed the informed consent. Exclusion criteria were as follows: (1) patients who did not meet the above requirements; (2) those with nerve or mental dysfunction or handicapped; (3) known drug allergy or tolerance to study drugs; (4) renal insufficiency or abnormal liver enzymes; (5) acute or chronic knee infection; and (6) serious cardiovascular disease, diabetes, or uncontrolled angina. All patients were randomly divided into two groups. No significant differences in baseline demographics were observed between the two groups.

### Patient grouping

A total of 110 patients who were scheduled to undergo TKA were randomly divided into two groups, experimental group and control group. Injections in the experimental group contained 200 mg of ropivacaine, 30 mg of ketorolac, 5 mg of hexadecadrol, and 0.3 mL of epinephrine. These drugs were mixed in a sterile normal saline solution with a combined volume of 50 ml. The control group received an equal volume of a normal saline solution.

All patients received general anesthesia, and the same surgeon performed all surgeries. The quadriceps and retinacular tissues were infiltrated with 15 ml of the drug mixture while the cement was curing. The remaining 35 ml was used to infiltrate fat and subcuticular tissues. All patients received patient-controlled analgesia (2 μg/kg sufentanil and 0.2 mg/kg tropisetron mixed with sterile normal saline solution in a total volume of 100 ml), and we limited the drip rate to 2 ml/h.

Patients administered moderate NSAIDs based on their needs 6 h postoperatively.

All patients were asked to perform ankle pump exercises during 24 h after surgery and active flexion movement 24 h after surgery. Pain scores, adverse reactions, range of motion, and use of NSAIDs were recorded every 8 hours. The averages of measurements were calculated. Patient satisfaction was monitored at the 7$^{th}$ day after surgery.

### Observation indexes

Pain scores were measured using numeric rating scale (NRS) scores, where 0 indicated no pain and 10 indicated the worst imaginable pain. We recorded the pain score, range of motion, and NSAID use at 12 h, 24 h, 48 h, 72 h, 4 days, 5 days, 6 days, 7 days, and 14 days after surgery. A number of reports of nausea, vomiting, and other adverse reactions were recorded during hospitalization. Evaluations of satisfaction including pain control satisfaction, hospitalization days, general satisfaction, and functional recovery were recorded at the 7$^{th}$ day after surgery.

### Discharge criteria

Patients were permitted to leave the hospital when they achieved −5°−0°−i extension and 80° of flexion; muscle strength was >4; spirit, appetite, and sleep recovery returned to preoperative levels; there was no swelling, bleeding, exudate, and other signs of infection; and after mastering knee functional exercises.

### Statistical analysis

Enumeration data were evaluated using Chi-square test, and measurement data were analyzed using *t*-tests. All information was processed using SPSS version 22.0 (SPSS, Chicago, Illinois). Statistical significance was set at $P < 0.05$.

## Results

We found that NRS scores with activity in the experimental group were lower than the control group at 12, 24, 48, and 72 h [Figure 2 and Table 2], and NRS scores at rest in the experimental group were lower than the control group at 12, 24, and 48 h [Figure 3 and Table 3].

The experimental group had a larger range of motion at 12 h, 24 h, 48 h, 72 h, and 4 days postoperatively than the control group [Figure 4 and Table 4]. These differences were statistically significant ($P < 0.05$).

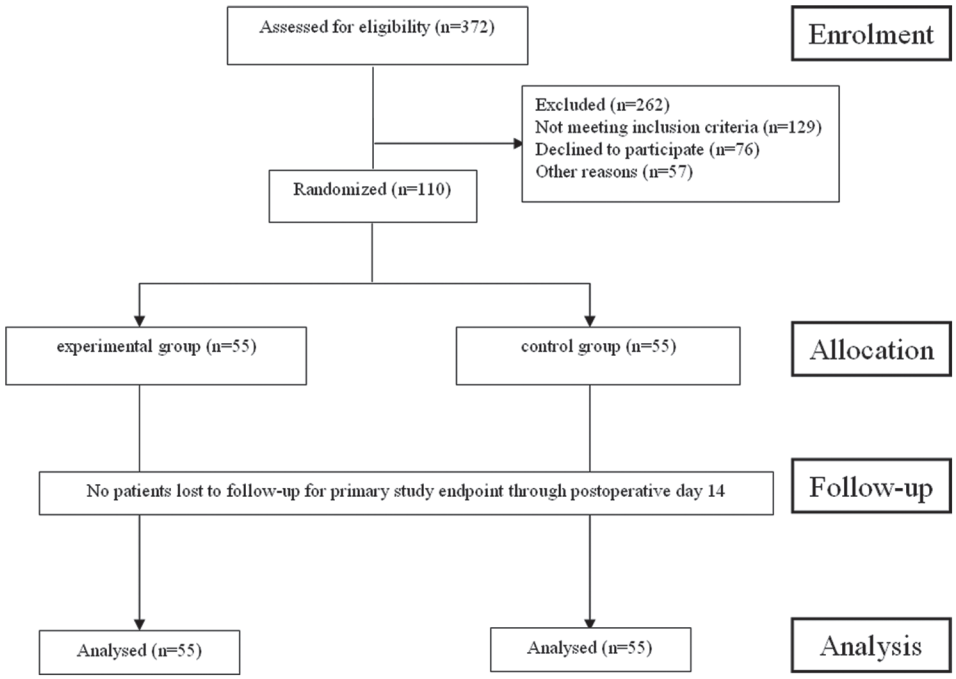


**Figure 1:** CONSORT study diagram

**Table 1: Demographic data for patients in the study ($\bar{x}\pm s$)**

| | Experimental group ($n$=55) | Control group ($n$=55) |
|---|---|---|
| Age, month | 63±11 | 65±9 |
| Gender (male:female) | 13:42 | 15:40 |
| BMI | 24.16±2.69 | 24.09±3.11 |
| HSS score | 49.45±12.96 | 49.02±14.23 |
| WOMAC score | 117.84±31.62 | 121.51±33.64 |

BMI=Body mass index; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index; HSS=Hematological scoring system

**Table 2: The numeric rating scale scores with activity ($\bar{x}\pm s$)**

| | Experimental group ($n$=55) | Control group ($n$=55) | $t$ | $P$ |
|---|---|---|---|---|
| 12 h | 6.83±0.78 | 7.25±0.80 | −2.832 | **0.006** |
| 24 h | 6.29±0.73 | 6.69±0.88 | −2.567 | **0.012** |
| 48 h | 5.68±0.72 | 6.05±0.82 | −2.483 | **0.015** |
| 72 h | 5.11±0.75 | 5.43±0.77 | −2.191 | **0.031** |
| 4 days | 4.43±0.65 | 4.54±0.82 | −0.757 | 0.451 |
| 5 days | 3.85±0.60 | 3.96±0.79 | −0.839 | 0.403 |
| 6 days | 3.31±0.60 | 4.47±0.74 | −1.219 | 0.225 |
| 7 days | 2.82±0.60 | 2.96±0.76 | −1.092 | 0.277 |
| 14 days | 1.86±0.41 | 1.84±0.36 | 0.245 | 0.807 |

Significant $P$ values are in italic bold

**Table 3: The numeric rating scale scores at rest ($\bar{x}\pm s$)**

| | Experimental group ($n$=55) | Control group ($n$=55) | $t$ | $P$ |
|---|---|---|---|---|
| 12 h | 5.10±0.89 | 5.58±0.94 | −2.788 | **0.006** |
| 24 h | 4.44±0.84 | 5.00±0.88 | −3.423 | **0.001** |
| 48 h | 3.88±0.63 | 4.28±0.75 | −3.018 | **0.003** |
| 72 h | 3.48±0.58 | 3.72±0.71 | −1.965 | 0.052 |
| 4 days | 3.05±0.54 | 3.26±0.60 | −1.893 | 0.061 |
| 5 days | 2.51±0.49 | 2.67±0.50 | −1.747 | 0.084 |
| 6 days | 2.12±0.46 | 2.23±0.46 | −1.240 | 0.218 |
| 7 days | 1.80±0.43 | 1.86±0.41 | −0.797 | 0.427 |
| 14 days | 1.24±0.23 | 1.21±0.22 | 0.549 | 0.584 |

Significant $P$ values are in italic bold

**Table 4: Range of motion after the operation degree ($\bar{x}\pm s$)**

| | Experimental group ($n$=55) | Control group ($n$=55) | $t$ | $P$ |
|---|---|---|---|---|
| 12 h | 15.33±3.92 | 13.04±3.70 | 3.253 | **0.002** |
| 24 h | 22.18±5.59 | 17.85±5.13 | 4.231 | **<0.001** |
| 48 h | 33.05±7.17 | 28.22±7.34 | 3.497 | **0.001** |
| 72 h | 45.16±7.87 | 40.05±9.64 | 3.045 | **0.003** |
| 4 days | 56.91±8.42 | 52.64±10.74 | 2.321 | **0.022** |
| 5 days | 68.82±9.26 | 65.76±10.14 | 1.650 | 0.102 |
| 6 days | 78.80±7.94 | 76.91±9.64 | 1.123 | 0.264 |
| 7 days | 86.00±7.72 | 86.53±8.70 | 0.336 | 0.737 |
| 14 days | 100.15±10.51 | 100.84±10.56 | 0.344 | 0.732 |

Significant $P$ values are in italic bold

The experimental group was treated with Celebrex (965 mg in total), and the control group was treated with 1325 mg for 1 week ($P < 0.05$). The experimental group was treated with Celebrex (1267 mg in total), and the control group was treated with 1678 mg Celebrex over 2 weeks [Figure 5 and Table 5]. These differences were statistically significant ($P < 0.05$). Meanwhile, the

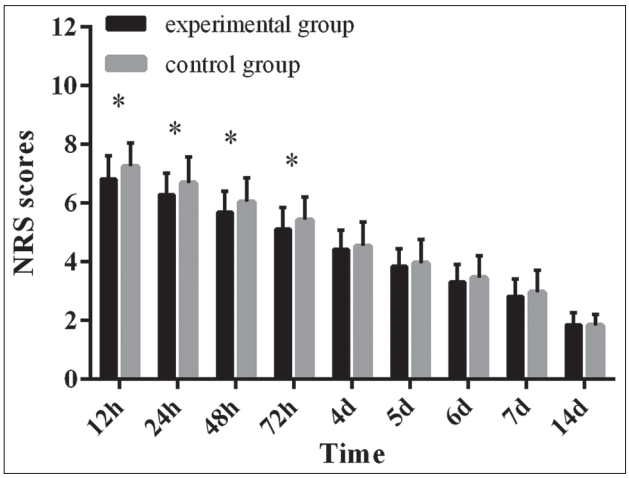


**Figure 2:** The numeric rating scale scores with activity (*compared with control group, $P < 0.05$)

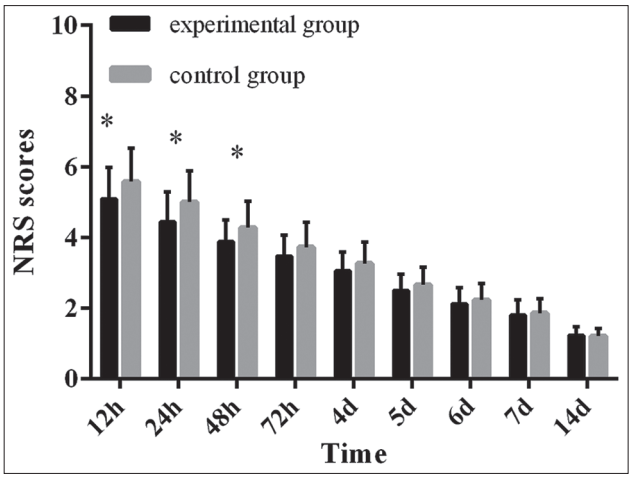


**Figure 3:** The numeric rating scale scores at rest (*compared with control group, $P < 0.05$)

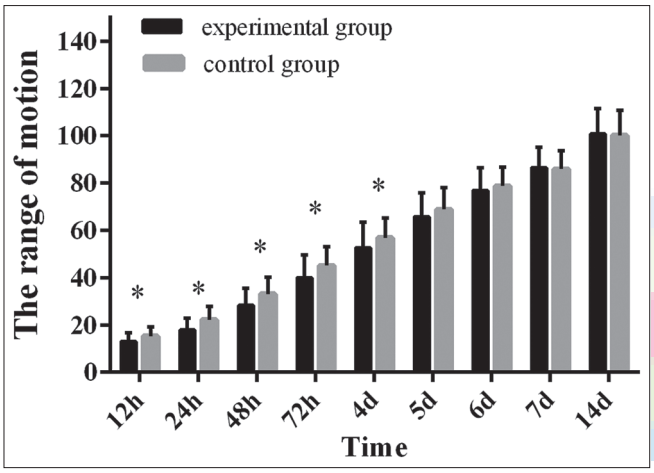


**Figure 4:** Range of motion after the operation. (*compared with control group, $P < 0.05$)

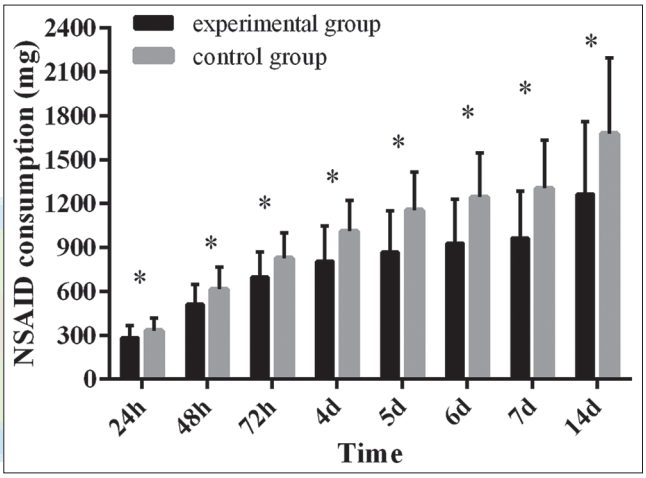


**Figure 5:** Total nonsteroidal anti-inflammatory drug consumption (*compared with control group, $P < 0.05$)

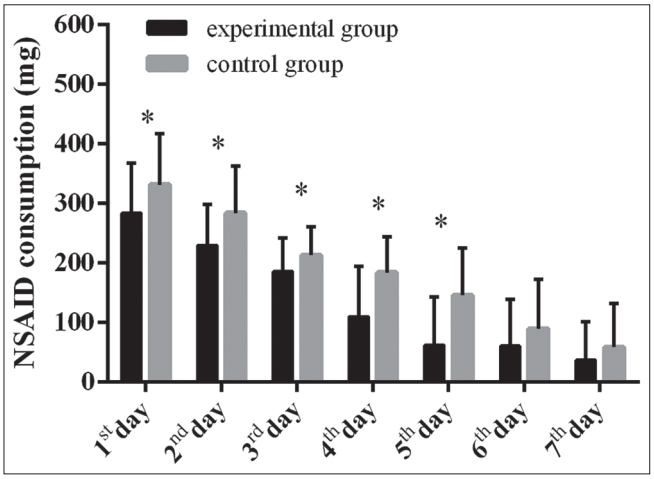


**Figure 6:** Nonsteroidal anti-inflammatory drug consumption per day (*compared with control group, $P < 0.05$)

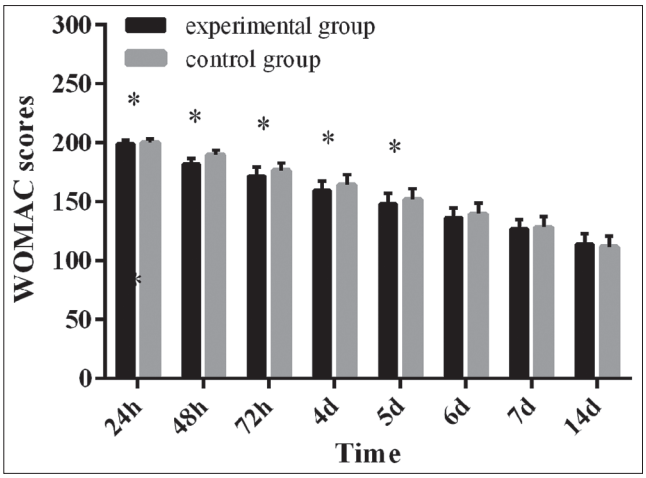


**Figure 7:** Western Ontario and McMaster Universities Osteoarthritis Index scores after the operation (*compared with control group, $P < 0.05$)

results of NSAID consumption per day demonstrated that the experimental group administered a dose of celecoxib every day that was far lower than the control group ($P < 0.05$) [Figure 6 and Table 6].

**Table 5: Total nonsteroidal anti-inflammatory drugs consumption per day (mg, $\bar{x}\pm s$)**

| | Experimental group ($n$=55) | Control group ($n$=55) | $t$ | $P$ |
|---|---|---|---|---|
| 24 h | 283.64±83.36 | 330.91±85.79 | −2.931 | **0.004** |
| 48 h | 512.73±136.16 | 614.55±152.06 | −3.700 | **<0.001** |
| 72 h | 698.18±171.58 | 827.27±172.62 | −3.933 | **<0.001** |
| 4 days | 807.27±238.71 | 1010.92±211.42 | −4.736 | **<0.001** |
| 5 days | 869.09±280.79 | 1156.36±258.75 | −5.580 | **<0.001** |
| 6 days | 929.09±299.80 | 1245.45±299.89 | −5.533 | **<0.001** |
| 7 days | 965.45±318.69 | 1303.64±329.96 | −5.467 | **<0.001** |
| 14 days | 1267.27±493.32 | 1678.18±518.08 | −4.260 | **<0.001** |

Significant $P$ values are in italic bold

**Table 6: Nonsteroidal anti-inflammatory drugs consumption per day (mg, $\bar{x}\pm s$)**

| | Experimental group ($n$=55) | Control group ($n$=55) | $t$ | $P$ |
|---|---|---|---|---|
| 1st day | 283.64±83.36 | 330.91±85.79 | −2.931 | **0.004** |
| 2nd day | 229.09±68.51 | 283.64±78.80 | −3.874 | **<0.001** |
| 3rd day | 185.45±55.84 | 212.73±47.35 | −2.763 | **0.007** |
| 4th day | 109.09±84.49 | 183.64±60.14 | −5.331 | **<0.001** |
| 5th day | 61.82±80.49 | 145.45±78.92 | −5.502 | **<0.001** |
| 6th day | 60.00±78.41 | 89.09±83.16 | −1.888 | 0.062 |
| 7th day | 36.36±64.88 | 58.18±73.76 | −1.647 | 0.102 |

Significant $P$ values are in italic bold

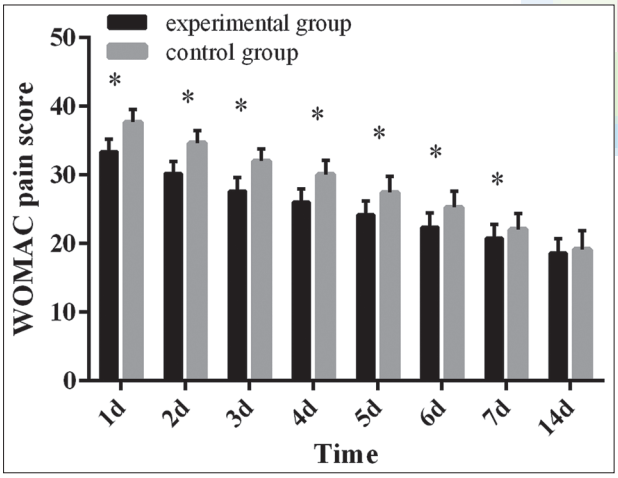


**Figure 8:** Western Ontario and McMaster Universities Osteoarthritis Index pain score after the operation (*compared with control group, $P < 0.05$)

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores of the experimental group were significantly better than the control group at 48 h, 72 h, 4 days, and 5 days [Figure 7 and Table 7]. These differences were statistically significant ($P < 0.05$). We made a special comparison of the pain parts in the WOMAC score. There was a significant difference between the two groups within 7 days ($P < 0.05$) [Figure 8 and Table 8].

**Table 7: Western Ontario and McMaster Universities Osteoarthritis Index scores after the operation ($\bar{x}\pm s$)**

| | Experimental group ($n$=55) | Control group ($n$=55) | $t$ | $P$ |
|---|---|---|---|---|
| 24 h | 199.01±3.128 | 200.00±3.405 | −1.591 | 0.114 |
| 48 h | 181.89±5.087 | 189.75±4.248 | −8.789 | **<0.001** |
| 72 h | 171.96±7.613 | 176.62±6.533 | −3.441 | **0.001** |
| 4 days | 159.42±8.078 | 164.55±8.322 | −3.279 | **0.001** |
| 5 days | 148.09±8.934 | 152.04±8.979 | −2.310 | **0.023** |
| 6 days | 136.58±8.326 | 139.75±9.037 | −1.909 | 0.059 |
| 7 days | 126.85±8.116 | 128.45±9.094 | −0.974 | 0.332 |
| 14 days | 114.09±9.139 | 111.69±9.147 | 1.377 | 0.172 |

Significant $P$ values are in italic bold

**Table 8: Western Ontario and McMaster Universities Osteoarthritis Index pain score after the operation ($\bar{x}\pm s$)**

| | Experimental group ($n$=55) | Control group ($n$=55) | $t$ | $P$ |
|---|---|---|---|---|
| 24 h | 33.41±1.810 | 37.69±1.876 | −12.177 | **<0.001** |
| 48 h | 30.21±1.782 | 34.65±1.797 | −13.021 | **<0.001** |
| 72 h | 27.64±1.984 | 32.01±1.814 | −12.061 | **<0.001** |
| 4 days | 26.01±1.993 | 30.07±2.096 | −10.405 | **<0.001** |
| 5 days | 24.20±2.040 | 27.44±2.360 | −7.706 | **<0.001** |
| 6 days | 22.38±2.097 | 25.28±2.316 | −6.884 | **<0.001** |
| 7 days | 20.78±2.001 | 22.05±2.298 | −3.114 | **0.002** |
| 14 days | 18.59±2.137 | 19.16±2.747 | 1.206 | 0.231 |

Significant $P$ values are in italic bold

The length of postoperative hospital stay was significantly different. Hospital stay in the experimental group was 9.25 ± 1.99 days and 10.44 ± 2.62 days in the control group ($P < 0.05$).

We found that postoperative pain satisfaction was significantly higher in the experimental group than the control group. However, no significant differences in the degree of satisfaction of the hospitalization days, general satisfaction, and functional recovery were observed.

## Discussion

Adequate postoperative pain control in TKA patients during postoperative functional recovery is very important, and a great analgesic effect can help patients relieve pain, get out of bed earlier to exercise, restore knee joint function, and prevent the formation of deep vein thrombosis (DVT).[7] Severe pain leads to prolonged hospital stays and increased opioid use. Many treatment options for TKA postoperative analgesia exist, but all these options have limitations. Epidural analgesia easily causes complications, such as nausea, hypotension, and urinary retention. TKA patients often receive anticoagulant drugs to prevent DVT, but these agents increase the risk of operative bleeding.[8,9] The

effect of intravenous analgesia is poor, and patients are prone to respiratory depression, nausea, vomiting, itching, and sleepiness.[10,11] We compared resting and motion NRS scores, knee joint range of motion, time of active exercise, length of postoperative hospital stay, patient satisfaction, total NSAID consumption, and side effects between the two groups to identify more safe and effective perioperative analgesic methods. Our results demonstrated that multimodal analgesia for postoperative pain control exhibited good patient recovery and effectively reduced the use of NSAIDs, which may cause serious side effects. The defects of this study are the short-term patient follow-up, and patients may not effectively evaluate their situation and NSAID drug use.

Our study found that NRS scores with activity were lower in the experimental group than the control group at 72 h, and NRS scores at rest were lower in the experimental group than the control group at 48 h. Some results in the literature are different.[10-14] Busch *et al*. found that the combination of ropivacaine and ketorolac tromethamine as a periarticular multimodal drug injection effectively reduced the intake of opioids, and postoperative NRS scores at 6, 12, and 24 h were significantly lower than the control group.[10] Todd and other researchers used a randomized, double-blind controlled study and found that the combination of ropivacaine, adrenaline, and ketorolac tromethamine exhibited a better effect than the use of ropivacaine and epinephrine alone,[11] and the former combination effectively reduced the amount of morphine for analgesia. Dexamethasone as a long-term glucocorticoid exhibits strong anti-inflammatory effects. Ropivacaine alone or bupivacaine combined with dexamethasone prolongs the effect of local anesthetics.[15] In addition, the differences in NRS scores in experimental group were subtle between different post-operation time points, although they might be significantly different. This is because the periarticular multimodal drug injection effect is relatively short. We also noted that the effect of postoperative analgesia between the two groups is subtle, which indicates that intraoperative periarticular multimodal drug injection may not be sufficient to completely control postoperative pain in TKA patients. Therefore, different drugs and drug delivery exhibit different effects. These differences require further research. All patients reported mild pain after 1 week, which supports that periarticular multimodal drug injection exhibited no long-term effects.

Patients with better pain relief exhibit improved postoperative motion. This study demonstrated that the experience of the experimental group patients within 4 days after surgery was better than the control group, but differences between the two groups disappeared after 4 days. In particular, we studied the pain part of the WOMAC pain score, and there was a significant difference within 7 days. There was no significant difference between the stiffness and the functional part. Early postoperative exercise is beneficial for patients with postoperative rehabilitation, and it avoids complications, such as DVT.[16-19] Sochart and Hardinge demonstrated that active or passive movement of postoperative lower limb increased blood flow.[20] Therefore, early postoperative activity is beneficial to reduce the occurrence of DVT and prevents the occurrence of emergency, such as pulmonary embolism.

We focused on the use of NSAIDs after surgery. Celecoxib capsules are a relatively new selective cyclooxygenase-2 (COX-2) inhibitor that primarily inhibits a COX-2 zymoprotein to block the synthesis of prostaglandins and achieve anti-inflammatory effects. Numerous studies demonstrated that celecoxib capsules are a new relatively selective COX-2 inhibitor, and patients who received celecoxib exhibited a reduced incidence of nausea and vomiting (28%). However, no research used large samples to demonstrate a reduced incidence of the side effects of celecoxib.[21] The side effects of postoperative celecoxib analgesia remain a problem that is difficult to ignore.[21,22] The results demonstrated that the experimental group ingested much less celecoxib than the control group. Six patients in our study reported nausea and vomiting in the experimental group, compared to seven patients in the control group, and no cardiac or central nervous system toxicity was observed. There were no significant differences between the two groups, and long-term side effect needs further study. However, previous studies suggest that the long-term use of NSAIDs significantly increased the incidence of adverse reactions.[23] Periarticular multimodal drug injection significantly reduced the intake of NSAIDs, which reduced NSAID-induced complications.

We used a digital classification method for the patients to evaluate all aspects of satisfaction during hospitalization. We found that postoperative pain satisfaction of the experimental group was significantly higher than that of the control group, but no significant differences existed in the degree of satisfaction with the number of hospitalization days, general satisfaction, or functional recovery. This result may be related to a variety of factors in postoperative functional exercise, drug use, care, and other relevant issues. Pain is only one factor. These results suggest that we cannot focus on only pain control after surgery in TKA patients and that a variety of measures should be used to improve the prognosis of patients and comprehensive quality of life.

Therefore, periarticular multimodal drug injection is a simple, safe, and low-cost surgery that effectively reduced the pain of patients after TKA,[24] and this method effectively advanced the time that patients began joint exercises, reduced the incidence of postoperative complications, improved joint function recovery, and shortened hospital stay. Local dosing in the knee joint largely reduced the intake of NSAIDs, which reduced NSAID-induced damage to the digestive tract and kidney. Multimodal analgesia after surgery was an effective treatment in the right patient and reduced complications.

## Conclusion

Intraoperative periarticular injection with multimodal drugs signifi cantly relieved pain after surgery and reduced the requirements for NSAIDs. This injection also improved patient satisfaction and the range of joint motion with no apparent risks following TKA.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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